TECHNOSPHERES™ FOR PULMONARY AND NASAL APPLICATIONS

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INTRODUCTION

Technosphere™ is a novel and versatile drug delivery system. Technospheres have been used to stabilize and deliver peptides, proteins, and small organic molecules via pulmonary (1), oral (2), subcutaneous (3), and intravenous (4) routes of administration. They are composed of diketopiperazine derivatives that self-assemble into 2 μm spheres at low pH (5,6).

Technospheres prepared for inhalation have typical physical and aerodynamic characteristics that direct them to the deep lung. They have a mass mean aerodynamic diameter (MMAD) of 2-4 μm and a respirable fraction of delivered weight (RF%, <5.8μm) of approximately 60%, as measured by Anderson cascade impaction (7,8). Once on the lung surface, fast and efficient absorption of proteins and peptides into the systemic circulation has been demonstrated in several clinical studies (1,9).

The goal of this project was to produce larger Technosphere particles (10-100 μm diameter) for nasal inhalation (7,10,11). Decongestants and antihistamines are extremely bitter and liquid carry-over of current aerosols transports the drug to taste centers. We expect that dry powder formulations will reduce drug carry-over and more precisely target the nasal mucosa.

METHODS

Technosphere Preparation

Technosphere particles for inhalation were prepared by dissolving fumaric acid-derivatized diketopiperazine (fumaryl Technosphere or FTS) in an aqueous ammonia solution. A 10% (v/v) solution of acetic acid was prepared for precipitating the particles. The FTS and acid solutions were mixed and the formed Technospheres™ precipitated with a mean hydrodynamic diameter of approximately 2.0μm. Excess reagents and salts were removed by filtration and resuspended in fresh DI water. The slurry was then pelleted into liquid nitrogen and lyophilized to produce a light powder.

For nasal administration, the same general procedure was followed except that the FTS and acetic acid solutions were prepared in a cosolvent system of water and an organic solvent. After mixing the FTS and acetic acid solutions, an additional aliquot of glacial acetic acid was added to the mixture to induce precipitation. The washing, pelleting, and lyophilization steps were the same as above.

Scanning Electron Microscopy

Specimen mounts were prepared by spreading a drop of 0.1% poly-l-lysine over the surface of the mount. When dry, the Technosphere sample was sprinkled over the surface of the mount. The specimen was coated with 20nm carbon (Gatan 681 High Resolution Ion Beam Coater) followed by 20nm Gold/Palladium (Anatech Hummer x sputter coater). Specimens were examined using a JEOL JSM 6320F SEM with an accelerating voltage of 3.5-5.0kV.

Particle Size Distribution

The particle size distributions in aqueous suspension were determined from dynamic light scattering using a Mastersizer 2000 (Malvern Instruments Ltd., Malvern UK). A sample of the suspension was introduced via the Hydro 2000S(A) small volume sample presentation unit to attain an obscuration of approximately 20%. The data were analyzed using Malvern's general purpose model.

RESULTS

The size distributions in Figure 1 are representative of Technospheres precipitated with 10% acetic acid. Technospheres in this size range are ideal for pulmonary drug delivery and have been used for clinical trials. The addition of active pharmaceutical ingredients does not significantly change the

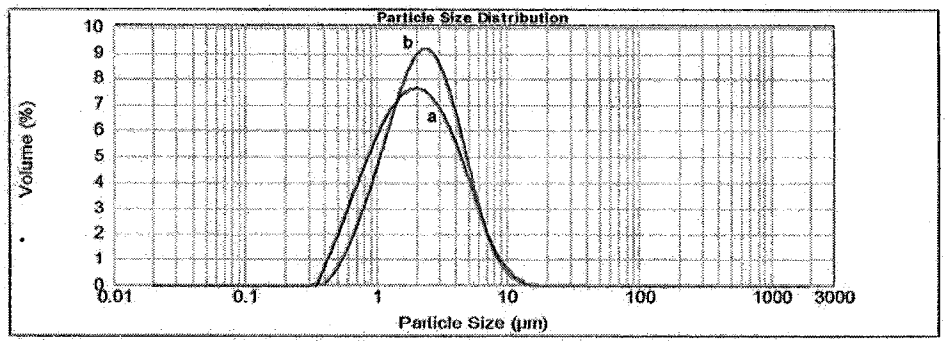

Figure 1 Overlay of hydrodynamic size distributions (Mastersizer 2000, Malvern Inst.) of Technosphere™ prepared for pulmonary delivery of insulin before (a) and after loading (b). Prior to loading, the spheres had a mean diameter of 2.5 µm, and after loading, 2.7 µm.

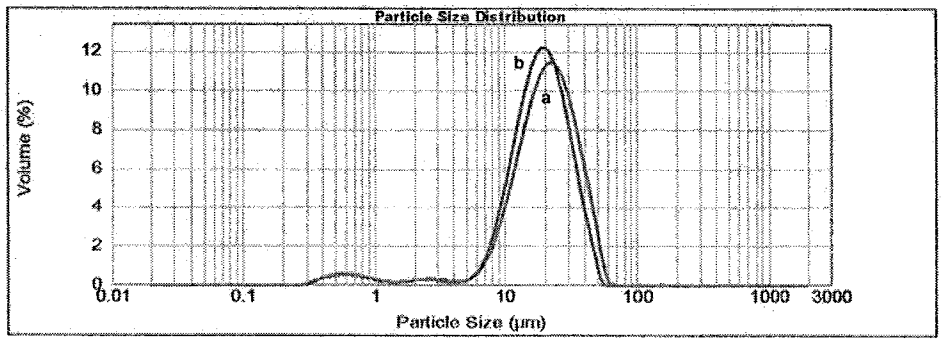

Figure 2 Overlay of hydrodynamic size distributions of Technospheres™ prepared for nasal delivery of an antihistamine before (a) and after loading (b). Prior to loading, the spheres had a mean diameter of 22.1 µm, and after loading, 19.7 µm.

size distribution of the particles in suspension. The two curves below correspond to "blank" Technosphere (a) and Technospheres with an 18% load of insulin (b).

Particle size distributions for these Technospheres again show that there is negligible difference between blank particles (curve a) and particles formulated with 14% load of a small organic molecule (curve b).

Scanning electron micrographs of Technosphere developed for inhalation and nasal application are shown in Figures 3 and 4.

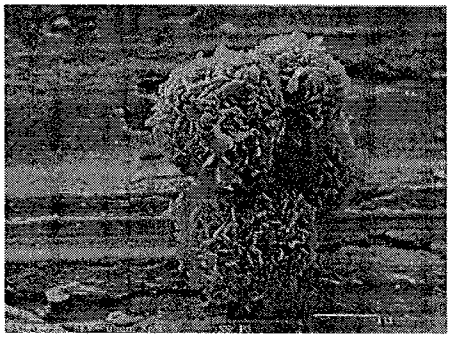

Figure 3 **Four Technospheres™ loaded with insulin (18% by weight) intended for pulmonary administration.**

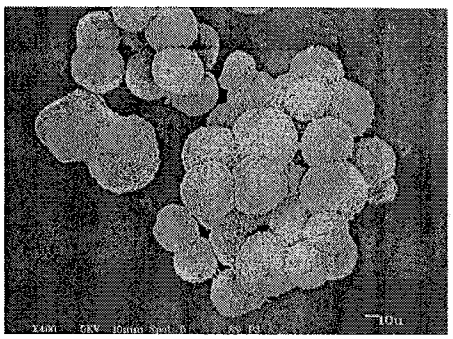

Figure 4 **Group of Technospheres™ intended for nasal adminstration, unloaded.**

Typical Technospheres precipitated with 10% acetic acid are shown in Figure 3; the average diameter of the primary particles is about 2 μm. In contrast, particles prepared for nasal application using a different cosolvent system have a mean hydrodynamic diameter of approximately 20 μm, with individual particles as large as 40 μm.

CONCLUSIONS

Technospheres may be formulated into small or large spheres for pulmonary, nasal, or other routes of administration by using different cosolvent systems. Loading of the spheres with pharmaceuticals does not significantly change the original size of the spheres as demonstrated by wet Malvern size distributions in Figures 1 and 2. Also, increasing the diameter of Technosphere from 2 to 20 μm, does not change the surface topography (Figure 3,4).

There are several potential advantages of Technospheres prepared for nasal inhalation over aqueous sprays. They may adhere to a specific site of action on the nasal mucosa, which can be expected to eliminate dripping of bitter tasting antihistamines into the throat. This approach should increase patient compliance and reduce the severity of side effects because a dose lower than that typically used for systemic delivery may be effective. Mixtures of different sizes may also be made to target the upper respiratory tract, as well as the deep lung. Such control over particle size makes Technosphere an extremely versatile drug delivery system.

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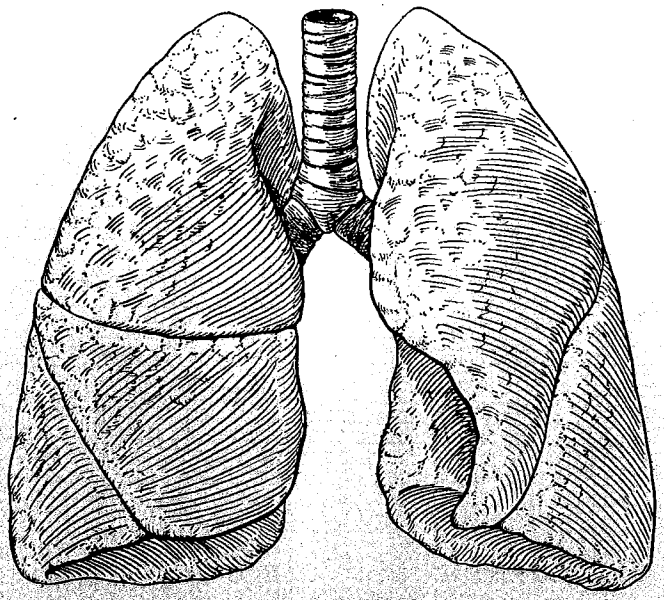
Respiratory Drug Delivery VIII

Biological, Pharmaceutical, Clinical, and Regulatory Issues Relating to Optimized Drug Delivery by Aerosol



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